A 15-Year-Old Girl with Weakness, Fatigue, Chest Pain, and Headaches

Robert Listernick, MD

A 15-year-old girl presented with 10 days of weakness, fatigue, chest pain, and headaches. Three weeks prior to presentation, she had an isolated episode of bilateral lower extremity weakness with paresthesias at school. She said she felt “as if my legs were going to give out.” The episode was self-limited and resolved within 1 hour. She has had multiple similar episodes and has collapsed on several occasions. She denies any pain, head trauma, or loss of consciousness. She also has had extreme fatigue during this time, which she describes as “coming out of anesthesia.” She has slept 20 hours per day and has only been to school for 1 to 2 days since her symptoms started over this period of time.

She also has had two episodes of hallucinations. During the first, she reported “seeing 7.5 doors in her parents’ bedroom.” She tried to walk through one, hit the wall, lost consciousness, and was found on the ground by her mother immediately after. She had another episode on the morning of admission where she woke up “completely paralyzed and a zebra named Tony in a Hawaiian shirt with a gold tooth was talking to her.” Although she was unable to move, she was able to call her mother on the phone during the episode and was able to move when her mother got to her room.

She denies any recent stressors but she just changed school districts and started high school. She reports having a good support network. She used to participate in a hip-hop dancing club but now only does it occasionally because she’s so tired that she comes home, lies on the couch, and naps every day.

Her past medical history is quite complicated. Many years ago, she was diagnosed as having idiopathic pulmonary hypertension and she is observed at an outside tertiary referral center. Her present echocardiogram shows mild right ventricular dilatation and hypertrophy, and mildly diminished right ventricular function; this is unchanged from previous echocardiograms. She has a history of heterotaxy syndrome and an interrupted inferior vena cava with abdominal situs inversus. She had scoliosis and has had a posterior fusion. She also has chronic thrombocytopenia (platelet counts around 110,000/mm³) that was found incidentally at age 12 years. Medications she is currently taking are tadalafil, bosentan, and fluoxetine.

On physical examination she is an alert, healthy-appearing girl. Pulse is 58 beats per minute, blood pressure is 100/60 mm Hg, respiratory rate is 16 breaths per minute, and pulse oximetry is 97% in room air. Her weight was in the 75th percentile and height in the 90th percentile. Both her general examination as well as her neurologic examination were entirely normal. She had no digital clubbing. Although she complained of weakness and dizziness and the feeling that “she’s going to fall over,” she was able to walk around the room with a normal gait.

The following laboratory tests were normal: hemoglobin, inflammatory markers, electrolytes, liver functions, thyroxine, thyroid-stimulating hormone, and B-type natriuretic peptide; troponin was negative. Platelet count was 88,000/mm³, which was her baseline count.

Robert Listernick, MD, moderator: Let’s start with her neuropsychiatric symptoms. How can you distinguish between organic and psychiatric disease in this type of situation?

James MacKenzie, MD, child psychiatrist: It can be extremely difficult. Whenever I’m sure that a child has a psychiatric disease, it turns out to be neurologic in origin and vice versa. Importantly, you have to resist the urge to say that just because a child is hallucinating, the etiology is schizophrenia. A psychiatrist can’t
Heterotaxy is a complication of anatomy involving the ventricles of the heart and the great vessels. For instance, in right atrial isomerism, there are often bilateral superior vena cava, anomalous pulmonary venous return, an absent coronary sinus, and a complete atrioventricular canal with pulmonary valve stenosis or atresia. In left atrial isomerism, we often see an interrupted inferior vena cava and a common atrioventricular valve in about 50% of the cases. Abnormalities of the conduction system are also common. This is a vast oversimplification of the heterogeneous nature of heterotaxy.

**Dr. Listernick:** She has normal cardiac physiology.

**Dr. Gossett:** Yes, but that is usually not the case. Most children who have heterotaxy syndrome and interrupted inferior vena cava have complex single ventricular hearts. In addition, it should be mentioned that sidedness of the lungs may or may not be altered irrespective of atrial anatomy.

**Dr. Listernick:** What about the abdominal organs?

**Ricardo Superina, MD, pediatric surgeon:** Absence of the spleen is most commonly seen in right atrial isomerism, whereas polysplenia is generally present in left atrial isomerism. The liver is unusually symmetric in the majority of cases. In addition, between 5% and 10% of cases of left atrial isomerism are associated with biliary atresia, usually extrahepatic.

**Dr. Listernick:** It should be remembered that children who have polysplenia are generally functionally asplenic despite the presence of multiple spleenules and are at risk for infections due to encapsulated organisms. What about the intestines?

**Dr. Superina:** Disorders of rotation can be seen in either form of isomerism. It’s somewhat controversial as to whether one should screen an asymptomatic patient with heterotaxy for a disorder of rotation.

**Dr. Listernick:** Why wouldn’t you look for malrotation?

**Dr. Superina:** In the asymptomatic child, performance of a Ladd’s procedure is controversial. In a Ladd’s procedure, we attempt to create adhesions by placing the small intestines on the right side and the colon on the left side of the peritoneal cavity. Although this fixes the intestines in place, the child remains at risk for developing small bowel obstruction from these same adhesions.

**Jeffrey Gossett, MD, pediatric cardiologist:** Heterotaxy is a complicated subject. In brief, it’s any combination of abnormal arrangement/sidedness of the thoracic and/or abdominal organs. The end result from a cardiac standpoint is the presence of either two right or two left sides, often marked by the presence of two right or two left atrial appendages. This, in turn, is associated with a number of variations of anatomy involving the ventricles and the great vessels. For instance, in right atrial isomerism, there are often bilateral superior vena cava, anomalous pulmonary venous return, an absent coronary sinus, and a complete atrioventricular canal with pulmonary valve stenosis or atresia. In left atrial isomerism, we often see an interrupted inferior vena cava and a common atrioventricular valve in about 50% of the cases. Abnormalities of the conduction system are also common. This is a vast oversimplification of the heterogeneous nature of heterotaxy.

**Dr. Listernick:** Is there testing that could help in the initial evaluation?

**Dr. MacKenzie:** Electroencephalogram (EEG) would be the test of choice. It’s quite useful distinguishing between a primary psychiatric disorder and an organic encephalopathy. The presence of slowing would strongly suggest the latter. Obviously, I would also do urine screening for drugs of abuse and any other testing as dictated by the history and physical examination (eg, neuroimaging, electrolytes, ammonia, antinuclear antibodies).

**Dr. Listernick:** There are a few other parts of her past history that we have to explore first. What is heterotaxy syndrome?

**Jeffrey Gossett, MD, pediatric cardiologist:** It’s true that the presence of two right or two left sides, often marked by the presence of two right or two left atrial appendages. This, in turn, is associated with a number of variations of anatomy involving the ventricles and the great vessels. For instance, in
Dr. Listerick: The last part of her past medical history is her idiopathic pulmonary hypertension (IPH). How do these children generally present?

Nicolas Porta, MD, neonatologist: Common presentations of IPH include decreased exercise capacity, chest pain, or syncope. These children may complain of vague chest pain or shortness of breath. They are often diagnosed as having exercise-induced asthma. Eventually, an electrocardiogram or echocardiogram performed due to chest pain leads to the correct diagnosis.

Dr. Listerick: Before labelling pulmonary hypertension “idiopathic” or “primary,” what underlying conditions need to be excluded?

Dr. Porta: Unrecognized cardiac disease with long-standing left-to-right shunts, such as from an atrial septal defect (ASD), is the most obvious category. With that said, there’s debate as to the role of ASDs in the pathogenesis of pulmonary hypertension. The shunting has to be very long-standing, so, for example, I would not call the ASD causal in a 10-year-old child.

Dr. Gossett: ASDs expose the pulmonary bed to high volume but low pressures. We see ASDs in all age strata that don’t lead to pulmonary hypertension. Untreated ventricular septal defects or patent ductus arteriosus are more likely to lead to pulmonary hypertension. Of course, those are rarely missed; we do see children from the developing world who have longstanding shunts and irreversible pulmonary hypertension.

Dr. Porta: Other causes of pulmonary hypertension include chronic obstructive sleep apnea, vasculitis such as lupus, chronic hypoxia due to unrecognized or undertreated pulmonary disease, portopulmonary hypertension, and chronic thromboembolism due to hypercoagulable conditions.

Dr. Listerick: Do you want to comment on treatment of IPH?

Dr. Porta: She is being treated with combination therapy of tadalafil, a longer-acting phosphodiesterase type 3 inhibitor, and bosentan, an endothelin receptor antagonist. These are less burdensome therapies for children as opposed to inhaled agents that must be taken several times daily because of short therapeutic half-lives or continuous subcutaneous or intravenous infusions in recalcitrant cases.

Estella Alonso, MD, pediatric hepatologist: This is all well and good, but I’d like to know why she has thrombocytopenia.

Dr. Listerick: I may not have had all the outside records, but I saw no attempt at divining an explanation. I’ll also point out that when she was admitted, her serum ammonia (which was drawn because of her psychiatric symptoms) was 53 mcMol/L (normal, 11-35 mcMol/L). These laboratory values coupled with her pulmonary hypertension suggested a possible diagnosis to me.

Dr. Alonso: Let’s briefly walk through this. Individuals who are thrombocytopenic are not making enough platelets, or are consuming them or sequestering them, most commonly in the spleen. Splenic sequestration of platelets often occurs in the setting of portal hypertension. Elevated ammonia may be seen in chronic liver disease, which also may cause portal hypertension. Pulmonary hypertension may be a manifestation of altered portal blood flow. We already know that she has vascular anomalies associated with her heterotaxy syndrome. It wouldn’t be a stretch to suggest that she has a portal vein abnormality leading to all these problems, tying all these seemingly disparate conditions together.

Dr. Listerick: This thought process led to the performance of an abdominal ultrasound in which an abnormality was noted. We didn’t have a radiologist available today, so Dr. Superina will take that role.

Dr. Superina: The ultrasound showed an abnormal connection between the portal vein and a systemic vein. The next study performed was computed tomography of the abdomen. First, we see polysplenia. The renal veins are draining appropriately into the inferior vena cava. The aorta is on the correct side of the body. The superior mesenteric vein that should normally continue up to the liver is being diverted posteriorly, communicating directly with the vena cava. There’s no apparent portal vein demonstrated. Ultimately, this was shown to be an Abernethy malformation.

Dr. Listerick: Abernethy malformation?

Dr. Superina: Without going into too much detail, it’s a congenital portosystemic shunt. We initially described two types of congenital portosystemic shunts. In type I Abernethy malformation, there is congenital absence of the portal vein with complete diversion of what would be portal flow into the inferior vena cava. In type II Abernethy, there’s a hypoplastic portal vein going to the liver that has a side-to-side shunt to systemic veins. This classification subsequently has been modified based on the specifics of the venous drainage. The details are probably too technical for this discussion.

Dr. Listerick: How is this generally discovered?

Dr. Superina: In most patients, it’s a serendipitous finding on either abdominal ultrasonography or echo-
cardiography performed for other reasons. Uncommonly, as in this girl, it comes to light due to a combination of symptoms such as might be seen with recurrent hyperammonemia. We haven’t seen frank psychosis; rather, we have seen children who most likely had a low-grade encephalopathy manifest mostly by attention-deficit disorder or learning disabilities.

**Dr. Listerick:** How does this portosystemic shunt affect the body’s physiology?

**Dr. Alonso:** Portal blood flow is extremely important for the health of the liver, allowing it to perform functions such as detoxification of ammonia and regulation of clotting factor synthesis. The liver also filters cytokines and other inflammatory mediators that arise from the splanchnic circulation. A systemic inflammatory state can develop that causes vasodilatation and hyperdynamic circulation; this is the physiology of cirrhosis. Some patients develop shunting of blood to the lungs and develop pulmonary hypertension rather than pulmonary vasodilatation. The pathogenesis responsible for the formation of pulmonary hypertension is not clear but may involve growth mediators from the gut that are not filtered by the liver. We don’t understand why some patients develop pulmonary vasodilatation and hepatopulmonary syndrome whereas others develop pulmonary hypertension.

**Dr. Listerick:** How do you treat this?

**Dr. Superina:** First, we have to accurately define the anatomy and the physiology of the blood flow. With the help of our colleagues in interventional radiology, a catheter is inserted into the inferior vena cava and into the shunt and a balloon is inflated to occlude the shunt. Contrast is injected to demonstrate the presence or absence of a rudimentary portal vein such as we see in this child. In many cases, we’ve found that the portal vein hypertrophies and we’re able to reverse the signs of the chronic portosystemic shunting. We measure the pressure in the splanchnic circulation; if it skyrockets, we attempt a banding procedure with gradual occlusion of the shunt in two or three sessions. Most of the time the shunt occludes successfully and the portal vein grows. If this doesn’t happen, we’ll have to repair the shunt surgically. We’ll have to see whether this has any effect on the pulmonary hypertension that has already developed.

**Dr. Listerick:** Incredible. Thanks everyone.

### Key Learning Points

1. Electroencephalogram is useful for distinguishing between a primary psychiatric disorder and organic encephalopathy.
2. Heterotaxy syndrome refers to any combination of abnormal arrangement/sidedness of the thoracic and/or abdominal organs. The end result from a cardiac standpoint is the presence of either two right sides or two left sides. This, in turn, leads to a number of variations of anatomy involving the ventricles and the great vessels.
3. Children who have polysplenia are generally functionally asplenic despite the presence of multiple spleenules.
4. Secondary causes of pulmonary hypertension include chronic left-to-right shunting due to unrepaired congenital heart disease, chronic obstructive sleep apnea, vasculitis such as lupus, chronic hypoxia due to unrecognized or undertreated pulmonary disease, portopulmonary hypertension, and chronic thromboembolism due to hypercoagulable conditions.
5. Abernethy malformation is a congenital portosystemic shunt in which there is diversion of portal blood flow into the systemic circulation. This may lead to low-grade encephalopathy such as attention-deficit disorder or learning disabilities due to chronic hyperammonemia, hepatopulmonary syndrome due to increased pulmonary blood flow, and shunting or pulmonary hypertension.